REMARKS

Claims 1-20 are pending in this application. There are no amendments to the claims. The species under examination are:

- Claim 4: *mesenchymal stem cells*
- Claim 6: CD90
- Claim 7: cardiomyocytes

Further consideration and allowance of the application is respectfully requested.

Priority:

The Office Action indicates that the reference to priority applications should occur in the first sentence of the specification, but is still in the second paragraph.

Applicant notes that the application as published already places the priority information in the first sentence of the specification. Nevertheless, to remove any uncertainty on this point, this paper formally contains an amendment to the specification that reverses the order of the first two paragraphs.

Request for rejoinder:

The current Office Action indicates that certain claims are objected to because they contain non-elected species. There is a request for rejoinder made previously in this application as part of the Response to the Restriction Requirement (April 7, 2003), which is still pending.

Applicant hereby renews the request for rejoinder, in view of the fact that no prior art has been identified that anticipates claim 1, which links each of the groups. The first cell population indicated in claim 1 links the cell types of claim 4 and the markers of claim 6. The second cell population in claim 1 links the cell types of claim 7.

MPEP § 803 indicates that a restriction requirement can only be imposed when examination of all the claims would impose a serious burden — regardless of whether the species are patentably distinct. 37 CFR § 1.141 allows applicant to present a reasonable number of species in a single application. Since claims 4, 6, and 7 each recite a reasonable number of species for each of the categories, and since no prior art has been identified, it would not impose a serious burden on the Office to examine all of the species together.

Accordingly, rejoinder and examination of all species in claims 4, 6, and 7 is appropriate. This obviates the objection to the claims indicated in the Office Action.

The previous objection to claim 20 for use of the word "their" has apparently been withdrawn, for which applicant is grateful.

Rejection under 35 USC § 112:

Claims 1-20 are still rejected under § 112 ¶ 1 as not being enabled by the specification to make and/or use the invention. The Office Action refers generally to the breadth of the claims, the state of the art, and the amount of guidance in the specification.

The section from line 1, page 3 to line 15, page 8 of the current Office Action is copied directly from the Office Action mailed June 18, 2003, and has been dealt with in the previous Response.

The section from line 16, page 8 to the bottom of page 15 provides some new commentary. However, the Office's position is still that the specification fails to meet the enablement requirements of § 112 ¶ 1 essentially because the specification does not include a working example of the invention.

This is not the correct standard. The relevant case law establishes that the specification *need not contain a working example* in order to comply with the requirements of § 112 ¶ 1:

> It is well established in the law that a specification can adequately describe the manner and process of making an embodiment of an invention, whether or not it has actually been conducted. Use of prophetic examples does not make a patent non-enabling. The burden is on the person challenging the patent to show . . . that the prophetic examples together with other parts of the specification are not enabling. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 224 USPQ 409 (Fed. Cir. 1984).
>
> Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided though broad terminology or illustrative examples. *In re Wright*, 27 USPQ2d 1510 (Fed. Cir. 1993).

hPS derived cardiomyocytes

The Office Action questions whether effective populations of cardiomyocytes can be made from hPS cells.

This Response is accompanied by a Declaration under 37 CFR § 1.132 from Dr. Joseph D. Gold, who directs the cardiomyocyte project here at Geron Corporation. Dr. Gold explains first of all that the essential steps in making cardiomyocytes from hPS cells (formation and culturing of embryoid bodies, and separation of cells on a density gradient) are described in the patent disclosure. It is expected that the implementation of any laboratory method will involve some degree of optimization (such as culture times and reagent quality) that would be solved as a matter of routine experimentation.

Applicant does not dispute that there may be other useful information available that may assist the user, but § 112 ¶ 1 does not require that the patent disclosure provide every little detail that may be useful in putting an invention into practice. Indeed, it is unnecessary and inappropriate for the disclosure to provide more information on the making of cardiomyocytes from hPS cells, since the generic invention (claim 1) is intended to be practiced with cells of any desirable therapeutic type, for which cardiomyocytes are exemplary. The specification supports the requirements of § 112 ¶ 1 for the making of cardiomyocytes by providing the essential steps, leaving the reader to fill in non-critical details from other references or by way of routine experimentation.

Dr. Gold goes on to explain that the embryonic stem cell derived cardiomyocytes have been transplanted into nude rats and shown to have desirable properties of a therapeutic cell population.

- The cells engraft into the cardiac tissue of the host and appear to expand over the 4 weeks of the experiment
- Engrafted cells can be identified by human-specific in situ hybridization, and by markers for cardiomyocytes (such as sMHC, and myosin light chain 2 v)
- Epithelial cells (expressing cytokeratins) disappear from the graft, while cardiomyocytes become more prominent
- Engrafted cardiomyocytes express the proliferative marker Ki-67 and take up BrdU, showing that they are actually proliferating

Thus, the hPS cell derived cardiomyocytes not only survive when engrafted into the myocardium, they have many other properties which appear to be superior to other cell types already in human clinical trials[1].

hPS derived mesenchymal cells

The Office Action implies that the data presented previously regarding the toleragenic properties of undifferentiated hPS cells, and early stage neural progenitors may not be shared by hPS derived mesenchymal cells.

Accompanying this response is a second Declaration by Dr. Anish Majumdar, providing data that show that hPS derived mesenchymal cells have the desired properties. The HEF1 cell line was made simply by plating out embryoid body cells, and selecting differentiated cells having an appropriate morphology. They were immortalized by transfecting with hTERT. This provided a convenient cell supply, but apparently did not otherwise alter the property of the cells. The phenotype of the HEF1 cells was CD29, CD44, CD71, and CD90 positive, and CD45 and CD14 negative — which is consistent with the marker profile indicated on page 13 of the specification, and with commercially available human mesenchymal stem cells (hMSC). The HEF1 cells also shared with hMSC the capability of forming osteoblast lineage cells.

Dr. Majumdar provides data from experiments in which the HEF1 cells were used to inhibit third party reactions between human dendritic cell stimulator cells and allogeneic T lymphocyte responder cells. Normally, DCs induce a high level of proliferation on allogeneic T cells. But both undifferentiated hPS cells and hPS derived mesenchymal cells have the ability to inhibit the reaction in a dose-dependent fashion.

This shows that the HEF-1 line (derived from embryonic stem cells and having mesenchymal characteristics) shares with other mesenchymal cells the immunological properties that make them suitable for promoting allograft survival, in accordance with the references provided in the previous Response[2].

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[1] Myocytes grown from striatal muscle (Phase I trial, Menasché et all, J. Am. Coll. Cardiol. 41:1078, 2003); and autologous bone marrow cells (Perin, Dohmann & al., Circulation 107:2294/03; Strauer & al., Circulation 106:1913/02).

[2] Seung et al. (J. Clin. Invest. 112:795, 2003); U.S. Patent 6,368,63; Kuhr et al. (Transplantation 73:1487, 2002); Barber et al. (Transplantation 51:70, 1991); Fontes et al. (Lancet 3434:151, 1994); and Rifle and Mousson (Transplantation 75 Suppl:3S, 2003).

Inducing tolerance in vivo

The Office Action implies that the second hPS derived cell population may not induce tolerance against the first cell population in accordance with the claimed invention, in view of a general uncertainty in the art regarding tolerance induction. A publication by Kuhr et al. (Transplantation 73:1487, 2002) is cited in support of the proposition that the mixed lymphocyte reaction is not reliable for determining responsiveness against kidney allografts.

This analysis is incorrect for a number of reasons:

- The question of tolerance induction is not relevant to the enablement of claims 1-13. In order for these claims to be enabled, it is sufficient for the specification to place into the hands of the readers each of the two matched cell populations. Whether or not the reader decides to use the cells for the tolerance induction strategy of claims 20-24, or the regenerative medicine strategy of claims 14-19, or for any other worthwhile proposes is entirely at their discretion.
- The assertion that the mixed lymphocyte reaction is not predictive of transplant rejection defies over 30 years of knowledge in the art. Jean Dausset won the Nobel Prize in Physiology or Medicine in 1980 for his discovery that typing and matching of human leukocyte antigens (HLA) was predictive of whether transplanted skin would be accepted. Information from the Nobel Prize website and articles about Dr. Dausset's contributions to the field are enclosed with this Response.
- The Kuhr publication relates to experiments in a dog model in which the donor and recipient animals were *already matched* for major histocompatibility antigens. Allograft reactivity was observed for reasons attributed to minor antigenic differences. However, had the dogs not already been DLA matched, then there would have been a more vigorous reaction both in the MLR and in the allograft response — confirming Dr. Dausset's discovery that typing and matching MHC antigens is useful for predicting allograft survival.
- The data from the mixed lymphocyte reactions provided with the 37 CFR § 1.132 Declarations by Dr. Majumdar, both on December 24, 2003, and accompanying this Response, is *not done for the purpose of tissue typing*. Rather, the undifferentiated hPS cells and the hPS derived mesenchymal cells are shown to *inhibit a mixed lymphocyte reaction amongst third-party cells,* showing the toleragenic properties of the mesenchymal cells.

- This invention helps solves *both* the problem of mismatch of HLA antigens in allograft tissue, *and* the mismatch of minor histocompatibility antigens (the source of allograft reactivity in the Kuhr reference). In a preferred embodiment, the first and second cell populations will be derived *from the same hPS cell line* (claim 2). This means that the two cell populations will match *exactly*, including both HLA, and minor histocompatibility antigens which were the source of alloreactivity in the Kuhr article. Thus, the first cell population is expected to tolerize against *all* the foreign antigens of the second cell population.

For all these reasons, the Office has failed to establish a prime facie case[3] that the use of the matched cell populations of this invention cannot be used to improve allograft survival in the manner taught in the disclosure.

In seeking to patent this invention, applicant does not propose to solve all the problems of tissue allografts in their entirety. As for any type of human transplantation, the clinician will need to monitor each patient, applying a combination of strategies as needed to minimize transplant rejection and improve graft survival. The skilled reader will appreciate that the practice of this invention may comprise a strategy of specific immunotolerance in combination with standard therapeutically approved general immunosuppressive drugs, such as cyclosporin A. Nevertheless, the invention claimed in this patent application will have value to the patient whenever it lessens the extent or duration of other adjunct therapies, or renders adjunct therapies more effective or reliable.

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[3] The Office has the burden of showing that the invention is not adequately enabled by the application. *In re Wright*, 27 USPQ2d 1510 (Fed. Cir. 1993). It is incumbent upon the Office to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning. *In re Marzocchi* 169 USPQ 367, 370 (CCPA 1971). [A]ny party making the assertion that a U.S. patent specification or claims fails, for one reason or another, to comply with § 112 bears the burden of persuasion in showing said lack of compliance. *Fiers v. Revel.*, 25 USPQ2d 1602 (Fed. Cir. 1993).

In summary, the information provided previously in the prosecution of this application confirm:

1. Cardiomyocytes are a viable therapy for heart disease in human patients;
2. hPS cells and their derivatives have the properties needed in mixed lymphocyte reactions done in tissue culture to act as tolerizing cells; and
3. Mesenchymal cells obtained from other sources that have the same histocompatibility type as an allograft improve survival of the allograft.

This Response and the accompanying Declaration confirm:

1. Cardiomyocytes can be made from hPS cells in the manner indicated in the specification
2. Cardiomyocytes *made from hPS cells* are *suitable for transplantation* in preclinical animal models
3. Mesenchymal stem cells *made from hPS cells* have the ability to inhibit a third-party mixed lymphocyte, demonstrating that they have *toleragenic properties that can be used for improving allograft survival* according to this invention.

Thus, the making and using of toleragenic and therapeutic cell populations according to the claimed inventor is fully enabled by the specification as filed. Withdrawal of this rejection is respectfully requested.

Conclusion

Applicant hereby offers to file a Request for Continued Examination under 37 CFR § 1.114, so that the Examiner may have the time and resources to reconsider the technical and legal aspects of these remarks and the accompanying Declarations in full.

Applicant respectfully requests that all outstanding objections and rejections be reconsidered and withdrawn. The application is believed to be in condition for allowance, and a prompt Notice of Allowance is requested.

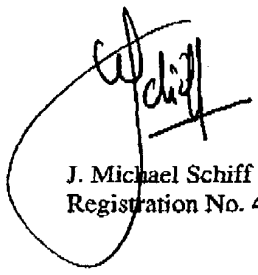
In the event that the Examiner determines that there are other matters to be addressed, applicant hereby requests an interview by telephone.

Fees

Enclosed with this Amendment is authorization to charge the Deposit Account for the extension of time.

Should the Patent Office determine that a further extension of time or any other relief is required for further consideration of this application, applicant hereby petitions for such relief, and authorizes the Commissioner to charge the cost of such petitions and other fees due in connection with the filing of these papers to Deposit Account No. 07-1139, referencing the docket number indicated above.

Respectfully submitted,



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June 29, 2004

JEAN DAUSSET

1980 Nobel Laureate in Medicine

for their discoveries concerning genetically determined structures on the cell surface that regulate immunological reactions.

Background

Born: 1916
Residence: France
Affiliation: Université de Paris, Laboratoire Immuno- Hématologi, Paris

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- Prize co-recipient: George D. Snell

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BARUJ BENACERRAF

1980 Nobel Laureate in Medicine

for their discoveries concerning genetically determined structures on the cell surface that regulate immunological reactions.

Background

Born: 1920
Place of Birth: Caracas, Venezuela
Residence: U.S.A.
Affiliation: Harvard Medical School, Boston, MA

Featured Internet Links

- Prize co-recipient: Jean Dausset
- Prize co-recipient: George D. Snell

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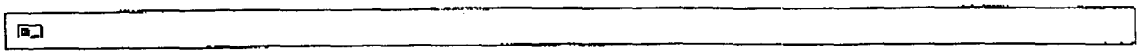

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GEORGE D. SNELL

1980 Nobel Laureate in Medicine

for their discoveries concerning genetically determined structures on the cell surface that regulate immunological reactions.

Background

Born: 1903
Residence: U.S.A.
Affiliation: Jackson Laboratory, Bar Harbor, ME

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- Prize co-recipient: Jean Dausset

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attention. But the following year, evidence for a fourth quark was unearthed, a watershed event in quark history because from then on the particles were taken increasingly seriously. And in 1977, physicists reported on the possibility of a fifth quark. Since the unified theory has quarks coming in pairs, physicists suspect that a sixth variety is also waiting to be found, and Kobayashi and Maskawa's model has become a serious contender.

Another explanation for CP violation by way of gauge theories was made by Columbia's Lee, also in 1973. Although the particles are as yet unobserved, the unified theory as developed by Steven Weinberg of Harvard University and Abdus Salam of Imperial College, London, requires the existence of an altogether new type of particle called a Higgs boson. Lee suggested that if there were at least four such particles, another mechanism for CP violation would be opened up. Weinberg later worked out a more realistic model of this type.

Among the differences between the models stemming from gauge theories (which are often called milliweak theories of CP violation) and the superweak theory is that the former predict the observation of larger CP violating effects in more places than does the latter. Several extremely sensitive experiments are planned or under way to try to distinguish between the various models.

Interest in CP violation also revved up in the 1970's because of its implications for cosmology and the Big Bang model of the origin of the universe. The various conservation laws of physics had seemed to say that, in the Big Bang, equal amounts of matter and antimatter had to be created. Similarly, as the universe expanded and cooled, equal amounts of matter and antimatter would have to be annihilated, as in collisions between electrons and positrons where both are transformed into gamma rays. Yet, experimentally, the universe seems to be almost entirely matter, the only antimatter coming in cosmic rays and in accelerators. One consequence of CP violation is that particles and antiparticles do not have to decay by the same reaction at the same rates. Among the first published accounts of a way to incorporate CP violation into a model for a universe consisting of matter but not antimatter was that by Soviet dissident Andrei Sakharov in the mid-1960's.

In the mid-1970's, a number of grand unified gauge theories were proposed that attempted to encompass the strong nuclear, weak, and electromagnetic forces into one formalism. A fallout of some of these theories is that there is a new hyperweak force (even weaker than Wolfenstein's superweak force) that is responsible for the unequal decay of matter and antimatter. Several theorists have in the last 2 years constructed speculative models based on an assumed hyperweak force and CP violation that roughly account for the imbalance of matter over antimatter in the universe, provided that a period of thermodynamic nonequilibrium existed in the early hot universe when the imbalance was created.

Some physicists have speculated that the Royal Swedish Academy of Sciences placed considerable weight on the emergence of gauge theory models of CP nonconservation and on the cosmological connection in making the award to Cronin and Fitch. Physicists hope this is not true because the Cronin-Fitch experiment, they say, stands on its own. "It was such a beautiful and elegant experiment," said experimentalist Jack Sandweiss of Yale, "that it was the equivalent of listening to Rudolf Serkin play Beethoven."—ARTHUR L. ROBINSON

1980 Nobel Prize in Physiology or Medicine

Three immunologists win for their research on the identification and action of histocompatibility antigens

A story that began more than 40 years ago with the identification of the first transplantation antigen in mice has culminated in the award of the 1980 Nobel Prize in Physiology or Medicine to three immunologists. The Nobel Assembly of the Karolinska Institutet has cited Baruj Benacerraf, Jean Dausset, and George Snell for their work on "genetically determined structures of the cell surface that regulate immunological reactions."

The structures in question, called histocompatibility antigens, are best known for their role in triggering the rejection of transplanted organs by the immune system. Their discovery has helped transplant surgeons select for grafting organs that are more likely to be accepted by the recipient. But, in addition, the histocompatibility antigens determine whether an individual can mount an immune response to a given antigen. In this way, they can influence the individual's susceptibility to disease.

The early history of the discovery of histocompatibility antigens is intertwined with that of the Jackson Laboratory in Bar Harbor, Maine. The laboratory was founded in 1929 by C. C. Little as a center for the study of mammalian genetics. Snell, who at age 77 is the oldest of the three new laureates, went to Bar Harbor in 1935 and has spent his professional life there. He had previously worked at the University of Texas with Herman Muller, who won a Nobel Prize in 1946 for studies of the x-ray induction of mutations in the fruit fly.

After working for a time on the x-ray induction of mutations in mice, Snell decided in the mid-1940's to look for a new project, one consistent with his training as a geneticist and his location at Bar Harbor. And, he says, "I wanted in the long run for it to have a payoff."

He knew from the work of Little that a number of genes controlled the ability of mice to resist tumor transplants, but at that time the genes had not been isolated or identified. Snell decided to find a way to study the working of each transplant gene individually.

He proceeded, in the words of Elizabeth Russell, his longtime colleague at Bar Harbor, "to invent the idea of congenic mice." These are mice that are genetically identical except at the single locus or genetic region to be studied. They make it possible to follow the effects of a single gene in a constant genetic background, and today they are a mainstay of histocompatibility research. For this contribution, Frank Lilly, of Albert Einstein College of Medicine, describes Snell as "the father of modern immunogenetics."

Breeding congenic mice is a tedious business, requiring some 14 to 15 generations. Snell met with an immediate setback when the Jackson Laboratory was burned out in 1947. But, he says, "The thing did work. Over the years we identi-

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fied a group of about ten loci that control graft resistance." They were not all equally effective, however. "One stood out like a sore thumb in determining whether a graft was accepted."

In work performed in the late 1930's, Peter Gorer, of Guy's Hospital in London, had prepared an antiserum that reacted with an antigen found on cells from one mouse strain but not on cells from a different strain. He showed that the antigen, which he designated antigen II, was also involved in tumor graft rejection.

After World War II, Gorer, bringing his antiserum with him, went to Jackson Laboratory to work with Snell for a year. They found that the genetic locus coding for antigen II and the locus found by Snell to be so important for graft rejection were one and the same, and they gave it the designation H-2. The H stands for histocompatibility, a term coined by Snell in 1948 to denote the cell surface antigens that determine whether one tissue is compatible with another. Compatible tissues have the same histocompatibility antigens. Incompatible tissues carry different ones. If an attempt is made to transplant a tissue into an incompatible recipient, the tissue will be recognized as foreign by the recipient's immune system and will be rejected. The 2 refers to Gorer's antigen II.

Baruj Benacerraf

Jean Dausset

George Snell

Snell, in recognition of Gorer's contributions to the discovery of histocompatibility antigens, says, "I just wish Peter Gorer were still alive to share the prize." (Gorer died at age 55 in 1961, and Nobel Prizes are not awarded posthumously.)

Although H-2 was at first thought to designate a single gene, subsequent genetic analysis of transplant rejection showed that what was originally called the H-2 locus is in fact a complex of many closely linked genes. This gene complex is called the major histocompatibility complex (MHC) because of its dominant role in determining transplant rejection, and it is located on chromosome 17 of the mouse. Two loci, designated K and D, carry the genes specifying the tissue antigens involved in triggering graft rejection. Any of some 20 to 30 different alleles may occur at each locus. (Alleles are alternative gene forms that may occur at a single locus.) Among the many investigators who contributed to the development of this picture, in addition to Snell and Gorer, are D. Bernard Amos, of Duke University Medical Center; Edward Boyse, of Memorial Sloan-Kettering Cancer Center; Jan Klein, of the Max-Planck-Institut für Biologie in Tübingen; and Donald Shreffler, who is now at Washington University Medical Center.

Beginning in the late 1950's, evidence for a human analog of the mouse H-2 system began to accumulate. At that time Jean Dausset, who is now at the University of Paris and St. Louis Hospital, was studying the antibodies produced by patients with serious blood diseases. He found that the patients who had received many blood tranfusions, and had thus been exposed to foreign tissue antigens, made antibodies that reacted with antigens found on white blood cells from other individuals but not with those on their own cells. Several of the patients produced antibodies against the same antigen, which Dausset called Mac. According to Fritz Bach, of the University of Minnesota Medical School, "This was the first serum to define an HLA antigen and led in part to the definition of the histocompatibility system in man." (HLA is the designation for the human MHC.)

In the years since Dausset identified the Mac antigen, the similarity between the mouse H-2 complex and the human HLA system has become clear. But for a time in the 1960's the situation was highly confused. Many antigen systems were being identified, and it was not clear how they were related to one another or whether they were. Amos says, "Different people were using different techniques and sera to identify antigens. It was hard to know what was going on."

Amid the confusion, however, there were some highlights. For example, Jon van Rood, of the University of Leiden, described two tissue antigens that were allelic products of the same genetic locus, which he called the 4 locus. And Rose Payne, of Stanford University, found another allelic system of antigens, which she designated LA.

In 1965 Dausset, with Pavol Ivanyi and Dagmar Ivanyi, who were then at the Czechoslovak National Academy, contributed a report that, in Amos's view, pointed the way to a better understanding of the antigen situation. The investigators described a system that included some ten antigens and implied that the genetic region coding for the system, which they called Hu-1, contained subloci that each specified a limited number of antigens. "That took us aback," Amos recollects, "we knew that a number of the antigens were related, but we did not think they all were."

Confirming this hypothesis and understanding the gene arrangement in the human major histocompatibility complex would require a few more years of work and the contributions of many immunologists. Meanwhile, efforts were under way to use the already identified tissue antigens for improved transplantation of organs, particularly skin and kidneys. Investigators, including van Rood, Ruggero Ceppellini, of the Turin Institute of Medical Genetics, and Paul Terasaki, of the University of California Medical School at Los Angeles, were finding that graft survival was greater when the donor and recipient (who were generally siblings) shared the same tissue antigens. This was a strong indication that the antigens being detected did in fact determine tissue compatibility, even though the investigators had not yet fully sorted them out.

Clarification of the tissues antigen solution was greatly facilitated by the his-

tocompatibility workshops begun by Amos in 1964. At these workshops, which are still held every 2 to 4 years, researchers share their resources, including the reagents and antiserums that they use to identify antigens, and tackle the currently outstanding problems in histocompatibility research.

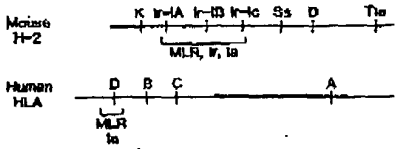
As it gradually developed, the picture of the human HLA system turned out to be just as complex as that of the mouse H-2 system. The LA and 4 loci—which are now designated HLA-A and HLA-B, respectively—are closely linked but separate loci within the HLA system. They are the human equivalents of the D and K loci of the mouse complex. The Hu-1 system described by Dausset and the Ivanyis included antigen products of both the HLA-A and HLA-B loci.

Identification of the HLA-A and HLA-B antigens has greatly improved the success of organ transplants, especially when the donor and recipient are related. The importance of matching for these antigens is less clear for transplants of kidneys from an unrelated donor. Recent results from a number of laboratories suggest that matching at another histocompatibility locus, designated HLA-DR (for D-related), may be more predictive of transplant success in these cases. The HLA-D locus (formerly the MLR locus) was brought under the human histocompatibility umbrella in the late 1960's by Bach and Amos.

But perhaps even more important is the role of blood transfusion to the recipient before kidney transplant surgery. A large body of data, principally accumulated by Terasaki and Gerhart Opelz at UCLA and recently extended by others, suggests that such transfusion improves the success of transplants from unrelated donors, possibly even overriding the effect of a tissue mismatch.

The use of histocompatibility antigens as a guide in transplantation can be considered extraordinary—important, but not likely to be needed by the vast majority of people. What the antigens do in everyday life, so to speak, is another matter. This role of antigen has been clarified by the work of Baruj Benacerraf, who is now chairman of the Department of Pathology and Fabyan Professor of Comparative Pathology at Harvard Medical School and president of the Sidney Farber Cancer Institute. Benacerraf has shown that genes located within the MHC control the many interactions among immune cells that are necessary for an individual to have an immune response.

According to Benacerraf, he began investigating the genetic control of immune responses "accidentally" in the early 1960's, when he was at New York University. He was working with Gerald Edelman, of Rockefeller University, on the analysis of antibody structures and was having difficulty because the antibody preparations then available consisted of heterogeneous populations of molecules. Benacerraf thought he might be able to produce a pure preparation of a single molecular species by immunizing animals (guinea pigs in the first experiments) with simple antigens such as polylysine, a synthetic polypeptide containing only the amino acid lysine. "What I found," Benacerraf explains, "is that some animals responded by making antibodies [to the antigen] and others did not. I thought this was an important observation and decided to investigate further." Thus he was diverted from antibody structure determination, for which Edelman shared the 1972 Nobel Prize in Physiology or Medicine with Rodney Porter, of the University of Oxford, England.



The MHC's of mice and men

Schematic comparison of the gene arrangement in the two MHC's. [Adapted from an illustration by Walter Bodmer of the Imperial Cancer Research Fund Laboratories in London; originally published by Academic Press]

Benacerraf showed that guinea pigs possess genes—called Ir (for immune response) genes—that allow them to make antibodies in response to some antigens. Shortly thereafter, Hugh McDevitt, of Stanford University, and Michael Sela, of the Weizmann Institute of Science in Rehobot, Israel, observed similar genes in mice. McDevitt then determined that they are located within the mouse MHC, not in the K or D region but in a region designated I. Benacerraf soon showed that the guinea pig Ir genes are in that species' MHC. In the human HLA system, the HLA-D region may contain the Ir genes.

Exactly how the Ir genes (or their products) exert control is not clear, but there is strong evidence that they do so by mediating the myriad interactions between immune cells. Although the B lymphocytes of the immune system actually produce the antibodies, other cell types are involved in the regulation of B cell activity. The principal regulatory cells belong to the T cell class of lymphocytes. Some T cells kill their target cells, others are "helper cells" that cooperate with B cells to elicit antibody production, and still others are "suppressor cells" that inhibit the activity either of other T cells or of B cells.

The Ir genes control only those antibody responses in which the helper cells cooperate. Benacerraf, with David Katz, of the Scripps Clinic and Research Foundation, showed that the T and B cells of mice cannot cooperate unless they both carry identical genes, which they mapped to the I region of the MHC.

The T cells themselves must be activated before they can turn on B cells. This requires still another cellular interaction, this one between T cells and macrophages that have picked up the triggering antigen. This interaction also depends on the macrophages and T cells having the same Ir genes, according to Ethan Shevach, of the National Institute of Allergy and Infectious Diseases, and Alan Rosenthal, who is now at the Merck Institute of Therapeutic Research in Rahway, New Jersey.

The best candidates for the cell surface components that participate in these interactions are a group of molecules called Ia (for I region-associated) antigens that were discovered by Shreffler and Klein. The Ia antigens are probably the products of the Ir genes, although this has not been proved.

Finally, the suppressor and helper T cells also communicate with their targets by releasing factors that either inhibit or stimulate them. The genes for these factors also lie in the I region of the mouse MHC.

If all this sounds complicated, it is. Benacerraf points out, "A very complex system is needed for controlling immune responses; the only parallel is the interactions in the nervous system." Nevertheless, he says, "We are finally beginning to understand the workings of the immune system and the intricate mechanisms for distinguishing self from nonself."

In addition, study of the MHC may ultimately shed new light on the etiology of a number of diseases that are not fully understood. Over the past 10 years many investigators have noted an association between a disease and one or another histocompatibility antigen. Many of these diseases are thought to be of autoimmune origin; that is, an immune attack is mistakenly directed at the body's own tissues. What is still lacking is an explanation of how the presence of a particular histocompatibility antigen might lead to the development of some pathological condition.—JEAN L. MARX

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that over the years, Wood probably has been blacked out under controlled circumstances more than anybody in the world, he is in fine health." Another official points out that such an experience "would probably not be allowed by a human studies committee today."

However, it was the large amount of data amassed about the cardiovascular system under stress that encouraged Mayo investigators to try to remain at the forefront of this area of research. "What these scientists learned," says a Mayo official, "became the basis for rapid developments in diagnostic right heart, left heart, and arterial catheterization. The procedures were done in Wood's Medical Sciences Building laboratory, using the centrifuge's sophisticated recording and monitoring facilities. Work in the centrifuge laboratory also led to perfection of the heart-lung machine . . . and development of computerized heart monitoring systems." All of this eventually led to the reconstructor.

The centrifuge itself was idle from 1947 until 1958, when it was recalled to active duty in the space age (*JAMA* [MEDICAL NEWS] 1973;224:1341-1343). It performed another 20 years for the National Aeronautics and Space Administration, but then had its final whirl and departed almost ignominiously in the fall of 1978—through a 3 m-wide hole chopped through the Medical Sciences Building's wall.

Doesn't the centrifuge deserve a place in a museum somewhere? Wood agrees that it does. But he says that unless the cost of transporting it to such a site can be solved, the historic centrifuge seems doomed to rust into oblivion, almost in the shadow of the reconstructor that has replaced it.—P.G.

Immunogenetics recognized by Nobel Prize

George Snell, DSc, Jean Dausset, MD, and Baruj Benacerraf, MD: These names, heretofore little known outside scientific circles, have in recent weeks become familiar to millions of people.

Born early this century in Massachusetts, France, and Venezuela, respectively, these three elder statesmen (aged 76, 63, and 60 years, respectively) of histocompatibility research will be in Stockholm Dec 6 to accept their joint Nobel Prize in Medicine.

The Royal Caroline Institute of Medicine notes that the prize—$211,000, to be split among the three scientists—is being awarded for elucidation of the histocompatibility gene complex, which controls most immunologic reactions. Knowledge of that complex, which specifies antigens on the cell surface, has had profound implications for the understanding of phenomena ranging from the rejection of kidney and bone marrow transplants to the pathogenesis of autoimmune disorders.

Snell's contribution, which led the way for histocompatibility antigen matching in transplantation, was his discovery of the histocompatibility or H-2 gene cluster in inbred mice. That cluster, known as the major histocompatibility complex, or its structural analogue is now known to exist in all mammals and may be present in all vertebrates. Snell uncovered it by backcrossing 12 to 14 mouse generations; developing congenic mouse lines in which the histocompatibility complex of one strain was introduced into the genome of another, and studying vulnerability to and rejection of transplanted tumors.

Snell told *JAMA* MEDICAL NEWS that his work began in 1935, when he arrived at The Jackson Laboratory in Bar Harbor, Maine, from the University of Texas. At that time, he picked up on some preliminary research conducted by the lab's founder, Dr Clarence D. Little.

Drs Snell (left) and Benacerraf (right).

Little had set up some cross-matches in mice and had found evidence of genetic factors operating in susceptibility to transplanted tumors. What was lacking was a method for identifying the individual genes governing that susceptibility. Snell began various studies with mice.

In 1947, a major disaster interrupted his work: The laboratory was devastated by a forest fire. "My strains and the processes of their production were lost," Snell said. But he remained undaunted, resuming his labors as soon as possible, two years later. Around the same time, Dr Peter Gorer of Guy's Hospital, London, spent a year at the laboratory. Gorer had found that susceptibility or resistance to transplants in mice was correlated with blood type.

"His gene and mine turned out to be one and the same," Snell explains. "Sally Lyon and Gorer both showed that there was not one gene but two in H-2,

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providing an early hint that this was a complex. Once the major congenic lines were established, we had strained pairs differing by a single gene. One locus [the H-2 locus] had a more important influence on graft resistance than the others."

In summary, Snell says, his work revealed the following three crucial pieces of information:

- The histocompatibility complex has a particularly potent effect on determining acceptance or rejection of transplanted tumors, measured in terms of graft rejection.
- The complex has at least two genetic loci.
- There are many alleles.

Thus, elementary as it may seem now, the import of the research was that organisms reject transplanted tumors not because they are tumors but because they originate in other organisms. As one text notes, "Nearly all the early workers labored under the delusion that they were studying cancer when they were, in fact, using tumors to study transplantation" (Billingham R, Willys S: *The Immunobiology of Transplantation.* Englewood Cliffs, NJ, Prentice-Hall Inc, 1971, p 5). However, says Snell, although the news that graft acceptance or rejection was an immunologic phenomenon was galvanizing, it was only with the discovery of the immune response area of the histocompatibility complex that the field "just exploded, and the most growth has occurred in the area of human research."

The first such research was undertaken by Dausset, who demonstrated the existence of the HLA complex, a human analogue to the H-2 complex, in in vitro studies. Dausset has described the striking biochemical and serological similarities of the two complexes but has noted, "Curiously enough, the beginnings of HLA were not inspired by H-2. The approach was quite different, since the first technique used in man, leukoagglutination, was devised to detect a state of autoimmunization" (Rose NR, Friedman H: *Clinical Immunology.* Washington, DC, American Society for Microbiology, 1976, p 787).

Another technique, now in general use, was to mix samples of leukocytes from numerous human subjects with sera from multiparous women (who are known to manufacture antileukocyte antibodies in many cases) and to detect HLA antigens through cytotoxicity assays. Studies of this type have continued, and new antigens and gene loci are added on a regular basis, usually following preliminary reports at World Health Organization workshops. All of this work began with Dausset.

Benacerraf's work was with animals (primarily mice and guinea pigs). By examining the animals' responses to simple amino acid polymers, he showed that an organism's response to foreign proteins is controlled by a small area of the histocompatibility complex dubbed the immune response area. This paved the way for an understanding of the association between the HLA complex and various disease states, that is, the knowledge that susceptibility to a given disorder may be genetically determined (as in the case of ankylosing spondylitis).

"Benacerraf's work led to the unraveling of what appears to be the major function of the histocompatibility complex, control of communication among the different cell types in the immune system," says David Katz, MD, a former associate of Benacerraf.

Katz, who is member and chairman, Department of Cellular and Developmental Immunology, Scripps Clinic and Research Foundation, La Jolla, Calif, continued, "The histocompatibility antigens are the 'fingerprints,' so to speak. The interactions among the different cells are controlled by the histocompatibility complex; the cells must interact properly for a proper response to foreign proteins to come about." Katz added, "The global significance of this work for medicine is that it now becomes apparent what role the histocompatibility complex plays in various disease states."

Katz and other immunologists, such as Irene Check, PhD, of Emory University, Atlanta, believe that the significance of Benacerraf's research for an understanding of cancer has been overplayed considerably in the press and that such an understanding is far down the road. Katz also notes, "A variety of other genetic mechanisms still have to be clarified in relation to diseases, such as certain autoimmune and immunodeficiency disorders."

Summarizing the work of the three Nobel laureates, Katz says, "Snell was the pioneer in the discovery of the system itself. He made that discovery many years ago with Gorer, when they carried out their studies constructing inbred strains of mice and examining the behavior of transplanted tumors. Then later Dausset demonstrated a comparable system in man. Benacerraf demonstrated the functional significance of the histocompatibility system, showing that it was present as a recognition system within the body and that immune response genes were involved."

Currently Snell, who earned his doctorate in science at Harvard, is senior staff scientist emeritus at The Jackson Laboratory. Among his many awards and honors is the Hektoen Silver Medal of the American Medical Association, which he received in 1955. He also is a member of the National Academy of Sciences.

Dausset, who received his medical degree at that University of Paris and later taught hematology there, is continuing his research in immunology at that university.

Benacerraf, who received his MD at the Medical College of Virginia in Richmond, is currently Fabyan Professor of Comparative Pathology, chairman of the Department of Pathology, and president and chief

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executive officer of the Sidney Farber Cancer Institute in Boston, as well as president of the International Union of Immunological Societies. Very recently he was named corecipient (with immunologist Henry G. Kunkel, MD, of The Rockefeller University) of the international Waterford Biomedical Science Award given by Scripps Clinic.

On the eve of their journey to Sweden, how do the two American Nobel laureates view their accomplishments?

Snell told *JAMA* MEDICAL NEWS, "I had put the Nobel Prize out of my mind as unlikely. Naturally you're overwhelmed at first. But there's no greater honor.

"I would like to stress what a fine place The Jackson Laboratory has been for my research. There were only seven researchers here when I came; now there are 500. It has been fun to see the laboratory grow, to see the field develop." In a telephone interview, Snell also credited many scientists throughout the world with making major contributions to the research for which he is to receive the Nobel Prize.

Said Benacerraf, also contacted by telephone, "I have nothing more to add at this time."

—by ELIZABETH RASCHE GONZÁLEZ

Do von Willebrand victims have less plaque?

There now is a registry of patients with the congenital coagulation disorder called von Willebrand's disease, particularly the more severe forms.

National Heart, Lung, and Blood Institute (NHLBI) officials in Bethesda, Md, say that when the needed technology becomes available—probably in the form of refinements in ultrasound equipment and techniques—some of these patients probably will be asked to take part in prospective studies on the development of atherosclerosis.

One hypothesis is that at least the severe forms of von Willebrand's disease (named for the Finnish physician who first reported it in 1926) may protect against atherosclerosis. If ultrasound monitoring lives up to expectations, it may be possible to study the blood vessels of such patients noninvasively to see if atherosclerotic plaque forms.

According to the NHLBI, 344 patients on the list are classified as having severe von Willebrand's disease, while 115 have less serious forms. Harvey J. Weiss, MD, professor of medicine at Columbia University College of Physicians and Surgeons, New York, began compiling the registry more than two years ago. At that time, he said that "while there obviously is an extremely high number of Americans with mild forms of von Willebrand's disease," it is not clear how many patients have the severe forms. He estimated in 1978 that there might be 400 of the latter.

While Weiss' estimate may be accurate, the overall incidence of this hemorrhagic disorder still is not known. But according to Harvey R. Gralnick, MD, chief of hematology at the National Institutes of Health Clinical Center, Bethesda, Md, there is evidence that von Willebrand's disease is the most common hereditary coagulation disorder in the United States.

For purposes of the NHLBI registry, severity of disease is determined by immunologic testing for factor VIII antigens and by assaying the capacity of plasma to cause normal platelet agglutination when the antibiotic ristocetin is present. The disorder, which affects both men and women, is characterized by a factor VIII deficiency, perhaps involving size, concentration, or content of what is called the von Willebrand-factor VIII glycoprotein, and by prolonged bleeding time owing to defective platelet adherence, perhaps involving insufficient enzymatic incorporation of the carbohydrate onto the glycoprotein.

If advances in ultrasonography or other essentially noninvasive techniques are forthcoming, a prospective study can compare the cardiovascular and cerebrovascular systems of persons with the disease with those of matched control volunteers. There are suggestions, primarily based on studies of a comparable disorder in pigs, that retardation of platelet aggregation in severe von Willebrand's disease may limit atherosclerotic buildup after arterial wall damage.

Still, those attempting any such prospective study face challenges. Ultrasonography may give some answers if sufficient resolution can be obtained to distinguish lesions of 1 mm or less within a vessel. Scientists working to refine ultrasound equipment and techniques are seeking clearer visualization of less accessible vessels, means of avoiding disruption of the signal by air spaces in the body, and better interpretation of the image so as not only to clearly identify what is being seen but to facilitate location of the precise spot in that subject again.

Cost of screening and getting volunteers for the study must also be considered.

A similar registry of patients with severe von Willebrand's disease is being compiled in western Europe. If eventually it is decided that a prospective study is feasible in the United States, the study might be done jointly with European investigators.

—by PHIL GUNBY.

Nobel Lecture, 8 December 1980

The Major Histocompatibility Complex in Man

Past, present, and future concepts

JEAN DAUSSET

As George Snell [1] so rightly said, the supergene, the major histocompatibility complex (MHC), is like a page from the nature book read outside of the context.

Today this context is beginning to be better understood. We would here like to recall the evolution of concepts regarding these molecular structures found in the membrane of cells. First, attention was centred on the almost botanical description of their genetic polymorphism. Then the spotlight was turned, for several years, on their importance in transplantation. More recently, their role in the immune response has become more and more apparent. This, however, is probably not the last stage in our search. We, as well as others [2–5], have suggested that the essential function of these structures resides in self-recognition. These structures are, in fact, the identity card of the entire organism.

We will discuss these four viewpoints successively. Far from being mutually exclusive, they are landmarks in the stages of our thought process as we have gained deeper knowledge of the subject.

First concept: Polymorphism and linkage disequilibrium

Polymorphism. Since Landsteiner's discovery of the first genetic polymorphism in man, knowledge of polymorphic genes has not ceased to increase and will continue to increase with DNA hybridization techniques. Most of these systems, however, are pauci-allelic and more often than not have one very frequent allele, one that is more infrequent, and a few variants. None of these can be compared with the extreme polymorphism of genes in the MHC of vertebrates, and particularly in the human lymphocyte antigen (HLA) complex.

The definition of this polymorphism began to emerge in three laboratories: in ours where the first antigen Mac (HLA-A2) was defined [6], in Van Rood's laboratory [7] with the 4a 4b series (Bw4, Bw6), and Rose Payne's and W. Bodmer's [8] with the two alleles HLA-A2 and -A3. Then, thanks to an intense international effort that has spanned more than 15 years and included eight workshops, the web began to be disentangled. The importance of this international effort, launched by Amos in 1964 [see Ref. 9], and followed by other workshops directed by Van Rood [10], Ceppellini [11], Terasaki [12], Dausset [13], Kissmeyer-Nielsen [14], Bodmer [15], and again Terasaki [16], cannot be over-emphasized and is to the credit of the whole histocompatibility community. The four presently well-defined, closely linked loci, HLA-A, HLA-B, HLA-C, and HLA-D/DR, have each from 8 to 39 codominant alleles, and the number of haplotypical or genotypical combinations already amounts to several million. It is very likely that other closely linked polyallelic loci will be discovered; similar, for example, to the various loci in the I region of the mouse. If one adds to this complexity the polymorphism of other genes in the HLA region, coding, for example, for factors C2, $C4^S$, $C4^F$, and Bf of complement, one reaches such levels of complexity that virtually every human has a different gene combination. If one considers all the genes of the human genome, it can be said that there is not and will never be on earth, apart from true twins, two identical people: every person is unique.

A question that immediately comes to mind is: Why is the MHC so complex? It is clear that a particular pressure was exerted on these genes to make them different and to maintain this differentiation. If it is true that these structures play a role in self-recognition and that they derive from primitive genes coding for surface molecules, then one can conceive of this diversity quickly becoming a necessity when living matter passed from the unicellular stage—or from a syncytium of identical cells

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able to fuse without harmful consequences—to the organized multicellular organism whose tissues must coexist and even cooperate and whose cells therefore cannot even merge with the cells of an organism of the same species.

Maintenance of this polymorphism is undoubtedly aided by the selective advantage given to the heterozygotes, possibly through the immune functions attributed to the MHC molecules in a subsequent stage of evolution.

The HLA system is now known to have two types of products that are very different from each other (their single nomenclature sometimes obscures this difference).

The products of the HLA-A, -B, and -C loci (Klein's class I [17]) are ubiquitous, being present at the surface of all (or almost all) cells of the organism. This wide distribution would suggest that they play a *very general* biological role.

In contrast, the products of the D/DR locus—and probably of the 'future' DR loci (class II)—exist only at the surface of certain specialized cells, essentially immunocompetent cells, a valuable piece of information with respect to their functions.

We must not neglect another valuable piece of information afforded by the major similarities between the class I products and immunoglobulins: the light chain (the β_2-microglobulin) as well as one of the domains ($\alpha 3$) of the heavy chain have significant similarities with the immunoglobulins and therefore suggest the possibility of a common ancestral gene [18, 19].

The light and heavy chains of the class II products bear no similarity either to the class I products or to the immunoglobulins. It can be said, therefore, that the products of the HLA complex are *bipolar* and are probably derived, by duplication and successive mutation, from two very distinct genes, the function and origin of which go far back in the evolution of the species.

At present, at least three variable regions on the heavy chain of the class I [20] products are known. In the most distal domain ($\alpha 1$) is the main variability zone (between amino acids 60 to 80), which probably corresponds to the serologically defined allelic epitope (individual antigenic determinant). This same domain also has (between amino acids 30 and 40) an apparently variable zone that is responsible for interaction with the influenza virus. In the median domain ($\alpha 2$) is a third variable zone (between amino acids 105 and 114).

The extreme frequency of cross-reactions between the various allelic molecules of each HLA locus is well known. Two interpretations that are not mutually exclusive are possible: the similarity in the structure of the allelic epitopes (*see* Colombani *et al.* [21]) or the existence of determinants common to two molecules but different from the epitopes; determinants which I. and Ivanyi [22], have called 'antigenic factors' (also known as supertypical antigens or public antigens).

According to our hypothesis, the molecules having an identical epitope—let us say, for example, A2—are not identical in their composition. Some may have one or more different antigenic factors. This variability may be found in the same population but is more often found in different populations [23].

This concept suggests that the various parts of an HLA molecule might have different functions (as is the case for the different portions of the immunoglobulin molecule). It has recently been shown that the interaction between the HLA molecule and the influenza virus does not take place at the level of the serologically distinguishable determinant since this virus has a different interaction with molecules which, nevertheless, have a serologically identical A2 determinant [24].

The same hypothesis could be applied to the DR molecules and could perhaps make it possible to solve the problem of the relations between the D and DR series. In effect, D might be no more than a variable part of the DR molecule having a stimulating function, since disassociated haplotypes do appear to exist—that is, where the determinant D is not the determinant usually found with the DR antigen [16, 25].

A second possibility, which should not be excluded, is that D in itself does not exist but is defined by an average of allostimulation due to a certain combination of alleles in the loci of region D, the linkage disequilibrium involving not only the DR locus but other loci as well, equivalent to IA, IJ, IC, IE of the mouse.

A second series of DR molecules is already in the process of being defined by both serological and cellular procedures. In particular an allelic SB series, centrometric in relation to the DR locus, has just been described [26, 27] through the use of mixed secondary lymphocytic cultures.

With regard to the genetic organization, we cannot yet grasp this in precise terms, but with the aid of modern DNA hybridization techniques it will not be long before we do understand it [28].

Linkage disequilibrium. The four loci of the HLA complex are closely linked on the short arm of chromosome 6 (21p). They are, however, sufficiently distant for relatively frequent recombinations to occur (0.8 per cent between A and B and 1 per cent between B and D/DR in man). This special situation seems presently to be virtually unique to human genetics. It is, moreover, accompanied by a particular phenomenon, which is the preferential gametic association between alleles of several loci of the same complex. A linkage disequilibrium is said to exist between these alleles. The phenomenon has given rise to numerous speculations.

Is this merely reminiscent of ancestral combinations (when populations were isolated some 2000 to 4000 years ago) that were revealed or increased by human migration? Could a mixture of populations temporarily set a certain haplotypical formula that would survive for only as long as was necessary for it to be dispersed through segregations occurring in successive generations [29]? Or is this linkage disequilibrium really a preferential association, that is to say, selected for the biological advantage or advantages it confers in a certain environment?

Of course, these two mechanisms can operate simultaneously.

One might ask whether the feature of linkage disequilibrium is specific to the MHC or whether it is a very general feature that recurs at other points of the genome.

HLA polymorphism and its linkage disequilibrium are valuable tools for anthropologists and epidemiologists. They allow the former to characterize a population; to discern its origin and draw up its genetic history. They allow the latter to compare HLA formulas and HLA haplotypes with the particular susceptibility of a population or groups of populations to certain diseases; and perhaps in the future they will be able to reconstitute major diseases and epidemics that have occurred in the past by observing the selections that have operated.

Finally, in formal genetics, the HLA complex is certainly the segment of the human genome that is best known and is a major example of our relating a human product to the sequence of the corresponding gene.

Second concept: Transplantation antigens

It is in such terms that these membrane structures are most often defined, because at the same time that genetic polymorphism was being elucidated, transplantation in humans was assuming great importance in therapeutics.

Our understanding of allogenic response in man has evolved rapidly. When only the HLA-A and -B antigens were known, allogenic response amounted to cytotoxicity on targets A and B. Thanks to admirable volunteers, the correlation between the survival of skin grafts and the number of HLA-A and -B incompatibilities was clearly demonstrated [30–33]. The same correlation was seen in recipients of related or non-related donor kidneys. This correlation, which was long debated, is no longer challenged; however, the benefit of compatibility limited to these two loci is very variable depending on the categories of patients.

When locus D was discovered [34, 35], its importance in transplantation was immediately suspected [36, 37]. In fact, it was shown in vitro that lymphocytic proliferation in allogenic culture was only possible when there was incompatibility at the D locus [38]. Clinically, a correlation has been found between the intensity of proliferation during the mixed lymphocytic reaction, that is, between the recipient and the related donor, and the survival of the graft. However, it has not been possible to apply this observation to the transplantation of non-related organs because of the time required for its elaboration.

In contrast, as soon as DR antigens [14, 15] could be detected by serological means—and thus rapidly—it became possible to use this new method of selection successfully. A DR incompatibility is accompanied by a drop in the survival rate of grafts, both skin [39, 40] and organ transplants [41,42]. In both cases there is a clear additive effect with those of the A and B incompatibilities (Fig. 1).

Incompatibility is in most cases both DR and D, and thus has two consequences:

(1) With DR incompatibility it provides a *target* for cytotoxic cells. DR antigens are true targets: they

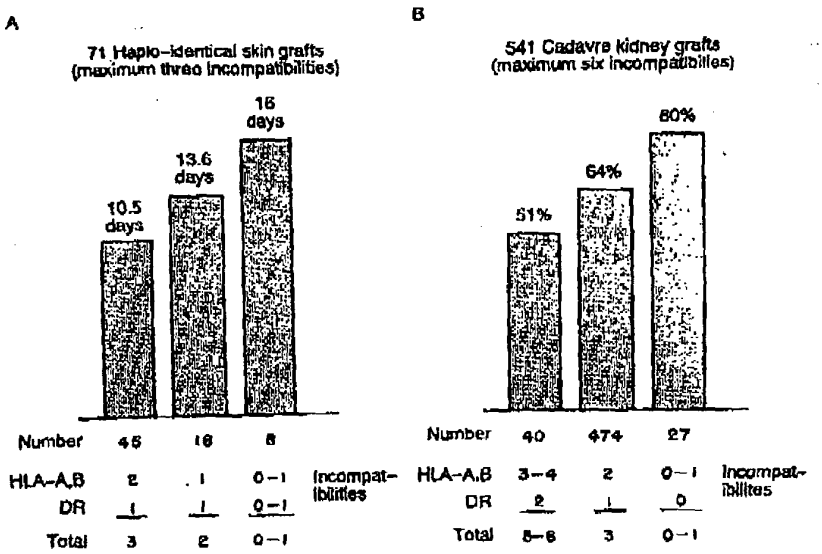

FIG. 1. Additive effect of HLA-A, -B and -DR incompatibilities. (A) Survival time (in days) of skin grafts done between HLA-haplo-identical individuals (most often child to father). Survival of the grafts increases progressively as the total number of HLA-A, -B plus -DR incompatibilities diminishes [30, 39]. (B) Percentage survival (at 2 years) of kidney transplants (done in the France-Transplant Network). The same tendency is observed, that is, survival is much improved where there are fewer total HLA-A, -B plus -DR incompatibilities.

do not behave like minor antigens because they do not need the HLA-A and -B identity between the killer cell and the target [43].

(2) It induces, by the D disparity, the appearance of auxiliary cells, some of which are helper cells and others suppressor cells. In the normal state, helper cells dominate suppressor cells. However, it must be made clear that in certain circumstances, the suppressor cells dominate the helper cells and the scale then tips in favour of tolerance.

It is possible that the indisputably beneficial effect of pre-operative transfusions is due to the development of suppressor cells or factors in the recipient [44]. In fact, with Sasportes and others [45, 46] we have shown that hyperimmunization against DR is accompanied by the in vitro appearance of a suppressive factor capable of producing a specific feedback inhibition on its own cells. The exact circumstances that cause the suppression in vivo to sometimes dominate immunity are unknown. However, it is known that in the monkey the beneficial effect of transfusions has been observed only where the animals are also immunosuppressed [47]. Recipients of kidneys are, so to speak, always immunosuppressed due to their renal insufficiency; this would explain why, in the course of transfusions, the immune balance leans in favour of suppression.

On the basis of the preceding considerations we have proposed [48] a theoretical plan, of necessity provisional, for the choice of blood donors for transfusion and organ donors. Without going into detail, it is based on the following principles:

(1) Before transplantation, a state of tolerance must be developed in the recipient and at the same time immunization against HLA-A and -B targets must be avoided. Thus, transfusions should be made with DR incompatible blood that is A, B compatible. The same DR incompatibility should be used constantly in order to increase the changes of the appearance of suppressive cells and the factors of the allogenic proliferation.

(2) In selecting the organ donor one must avoid providing targets against which the recipient could be immunized. Thus, priority should be given to HLA-DR compatibility in patients who have not produced antibodies against HLA-A and -B antigens in the course of transfusions (non-responder recipients). On the other hand, priority should be given to HLA-A and -B compatibility in those who have been sensitized in the course of pre-operative transfusions (responder recipients). Indeed, for the former there is little chance of immunization occurring against A or B antigens, but the appearance of helper cells and a supply of DR targets should be avoided. Conversely, in the responders, helper cells are already present and their action must be neutralized by not contributing incompatible A and B targets.

Very precise and detailed treatment protocols will be necessary to verify or disprove the validity of this plan.

Third concept: Role in the immune response

This third concept is essentially based on our knowledge of animals since systematic experiments are ethically difficult and thus rare in man [49]. Nonetheless, to date, the parallel with the H-2 complex is striking. Here again we find the *bipolar* division of the functions of the products of the HLA complex:

(1) Class I products appear to serve as targets when a cell is either infected by a virus or covered with a hapten.

(2) Class II products appear to serve as a regulator between the various cell subgroups involved in the immune response.

In both cases, a phenomenon of restriction is most often observed, that is to say, an identity with class I or II products is apparently necessary between the cooperating cells.

Thus a phenomenon of restriction exists in the cytotoxicity of a killer T-lymphocyte cell against a cell carrying a virus [50, 51], a hapten [52] such as DNP, or a normal antigen such as the H-Y antigen [53]. The killer cell must have at least one identity with the HLA-A and -B (class I) antigens of the target cell in order for the lysis to be effective, or else the killer must have matured in the presence of the histocompatibility antigens of the target.

Similarly, when an antigen such as PPD is presented by human macrophages [54], the presence of a DR identity (class II) is apparently necessary for the presentation to be effective and for lymphocytic proliferation to occur. This restriction is not absolute, however, and a certain number of proliferative reactions that can be explained by cross-reactions between DR antigens have been observed.

As in the mouse, where soluble factors carry antigens from the I region that convey a specific message to another T- or B-cell population, so in man there is evidence of a certain number of soluble factors of this type [55, 56]. Undoubtedly, when we have a better understanding of the various products of region D in man, numerous specific and aspecific factors, either restricted or unrestricted, will be described.

The restriction phenomenon is probably the most direct proof of the role of the products of the HLA complex in the immune response of man.

Indirect proof has been sought in the numerous associations between HLA and diseases. Based on the murine model, the first study of associations between HLA and disease was done in our laboratory on acute lymphoblastic leukaemia [57]. A slight but definite increase of A2 has now been demonstrated in numerous worldwide studies [58]. Likewise, the A1 antigen is slightly increased in Hodgkin's disease. These two observations would suggest that a gene acting on haematopoiesis may exist near locus A [58].

However, most of the diseases indisputably associated with HLA are neither tumorous nor obviously infectious [59]. These are chronic or subacute diseases having a definite familial though mild character, that are of unknown etiology and are not included in any of the major classifications. For a good number of these there is an obvious autoimmune component.

We will give only two examples to illustrate once again the bipolar nature of the functions of HLA products. In the first example, class I products may still be considered as possible targets; in the second example, class II products may be considered as regulators of the immune response.

Articular and more especially sacropelvic disorders that are strongly associated with B27 seem to require the molecule HLA-B itself to play an essential role. In fact, the same B27 antigen is found in a series of disorders (Reiter's syndrome, ankylosis spondylarthritis, psoriatic rheumatism) which tend to

affect the articulations of the sacrum and pelvis. Further, this same predisposition is found in all populations of the globe. However, it has now been clearly demonstrated that the same pathological manifestations can also affect a small number of individuals who are B27 negative. The B27 epitope is therefore not indispensable. At least two hypotheses may be advanced: either the responsible gene in all populations is strongly linked with the B27 antigen, or molecule B27 has a variable part (an antigenic factor) that is responsible for susceptibility; this antigenic factor would not always be present on all B27 molecules and could be found on other HLA molecules probably having cross-reactions with B27 (in keeping with our concept explained above).

It seems, moreover, that for these diseases there is a factor that triggers infection. In fact, it is known that some acute intestinal infections caused by Gram-negative bacteria as *Shigella*, *Salmonella*, and *Yersinia* are complicated by ankylosing spondylarthritis mainly in patients who are B27 positive. Recently, a direct relationship was suggested between the B27 antigen and a type of *Klebsiella* (*Klebsiella* B43). The antibodies against *Klebsiella* would be capable of recognizing specifically an antigen present on the lymphocytes of B27 positive patients affected by ankylosing spondylarthritis. Further, lysates from this infectious agent would be capable of transforming lymphocytes in B27 normal individuals and of making them sensitive to the antibodies against *Klebsiella* [60, 61]. Although clinically the link between a *Klebsiella* infection and ankylosing spondylarthritis is still unclear, this observation, not yet confirmed, suggests that certain infectious agents would be capable of modifying HLA antigens and of apparently making them similar to those in patients. It is not impossible that this type of mechanism may one day explain the linkages with other micro-organisms referred to above. These micro-organisms would be capable of modifying the B27 antigen and perhaps certain other HLA molecules as well (to take into account B27 negative patients), and of making them privileged targets for T-immune autolymphocytes. Although this hypothesis is enticing, it cannot yet explain the very special localization of lesions, since the B27 antigen, like all HLA antigens, is practically ubiquitous.

If we now consider disorders associated with HLA-D/DR, one is at the outset struck by the large number of them that are associated with Dw3/DR3 and, more especially in Caucasians, with the A1, B8, DR3 haplotype. For the most part, these are diseases with a strong autoimmune component and a low family penetrance, such as myasthenia gravis, Graves' disease, Addison's disease, Sjögren's syndrome, disseminated lupus erythematosus, and active chronic hepatitis. It appears that this haplotype, in strong linkage disequilibrium, has a gene or perhaps a series of genes that are conducive to autoimmunization.

Insulin-dependent juvenile diabetes (IDD), itself associated with A1, B8, DR3 and also with B18, DR3, and B15, DR4 is in this respect very instructive [62, 63]. The viral etiology of IDD is highly suspected: experimental models of the disease do exist and specific observations in some cases in man incriminate the B4 Coxsackie virus. One can therefore infer that the virus has destroyed a certain number of islets of Langerhans and triggered a process of cellular autoimmunity where cytotoxic lymphocytes persist in the organism against antigens modified by or associated with a virus. The disease would thus be self-sustained. In this hypothesis the D region products would have been incapable of inducing an adequate immune reaction against the virus causing the disease. In contrast, individuals who are DR2 positive (most frequently A3, B7, DR2), who appear to be 'protected' against IDD, would have a more effective immune response against the responsible agent.

This is only a working hypothesis, which would have the advantage of applying to other diseases associated with HLA-DR such as multiple sclerosis (DR2) and chronic polyarthritis (DR4) or juvenile rheumatism (DR5).

The reality, however, is certainly far more complex. In fact, in no case is the association complete with a DR antigen. This is generally explained by a linkage disequilibrium between a simple susceptibility gene for the disease and a DR allele. Here too, however, one might think that there are polymorphic parts to DR molecules other than the epitopes presently known and that these might have a particular immune function. Even better, it could be assumed that the interaction of two (or more than two) genes from the D region would be conducive to an adequate immune response. This interaction could take place in the *cis* position [64] between genes of the same haplotype (as in the interaction between I-A^b and I-E^b to form an I-E molecule in the mouse) or in the *trans* [65] position between two haplotypes (such as I-A^k and I-A^b complementation in the mouse).

As a corollary to these gene interactions we propose that each HLA haplotype, and especially those in

linkage disequilibrium that are found most frequently in the numerous diseases associated with HLA, has its own gene configuration that confers on it a particular capacity for immune response, which may be favourable in certain environmental conditions and unfavourable in others (for example the A3, B7, DR2 haplotype gives a susceptibility to multiple sclerosis and protects against IDD). Thus, each HLA complex would be composed of a set of genes that have subtle interactions among one another (such as gene C2 with the two C4 genes) thereby giving them a specific identity in immunological terms.

Likewise, every individual possessing two HLA haplotypes has his or her own immunological capacity which is conferred on him by the two particular haplotypical formulas inherited from his two parents, but which is also the result of the genetic interaction or complementation between these two complexes. Thus each individual has a personal immune response that makes him either susceptible or resistant to certain diseases. Here again each haplotypical combination may be beneficial or harmful depending on the type of challenge to which the individual is subjected.

In terms of the population, we can thus conceive that certain individuals are or were more exposed and thus are or were more easily eliminated than other individuals more resistant to past and present epidemic or endemic diseases. But it is not the same individuals who are susceptible or resistant to the different attacks; this is what makes the survival of a population possible, and thus the perpetuation of the human species.

Fourth concept: Self-recognition

MHC products are distributed on the surface of cells. Those of class I are virtually ubiquitous. Class II products may be found on immunocompetent cells but also on endothelial and other specialized cells. Their location suggests that they play a role in the social organization of cells of the same organism.

This assumption is strongly supported by the following observation: it appears to be necessary for MHC products to share an identity in order for cooperation to be established between two populations of cells in the same organism or in two different organisms. This is the restriction phenomenon which we discussed above, and which is valid for the two classes of products. Results confirming this apparent need for identity are accumulating very rapidly in both animals and man and are no longer limited solely to immunocompetent cells. The same is true, for example, in the adhesion phenomenon between fibroblasts and especially in the 'homing' phenomenon in ganglia. Degos and others [60] have observed that splenocytes injected intravenously must share an identity with the cells of the capillary endothelium with regard to class I products so that homing can occur. The identity of class II products does not intervene (Fig. 2).

We are thus faced with a very general phenomenon with such a consistent record that it is difficult to escape the conclusion that the two types of molecules have a common function. They could serve as a recognition signal (recognizers) among cells of the same organism; a signal necessary but probably insufficient to permit effective cooperation between the two subpopulations of cells because it would be the same, at least at class I, for all cells of the organism [2–5].

The passive or negative discrimination of self implies that the cells 'ignore' one another. This seems improbable in view of the cohesion of tissues and of their interaction. Without self-recognition, each specialized cell and each tissue would be isolated and incapable of surviving. These considerations thus suggest that self-recognition is an active phenomenon.

The subjacent mechanism of self-recognition is still unknown. At least three possibilities come to mind. The most orthodox is the complementarity between two different molecules. But one cannot exclude recognition by identity, whether that recognition takes place between two identical molecules or through a ligand. This fascinating problem has been discussed in detail elsewhere [67]. Suffice it to mention here just two remarks in relation to complementarity:

(1) If a second molecule (receptor) existed with the same immunogenicity as the HLA determinant, a second allelic system as complex as the former would have been found. To date no such system has been found. However, one should remain aware of the weak immunogenicity of the idiotypes which could represent these receptors.

(2) If the receptor and the determinant were coded by two different genes, any mutation and selection

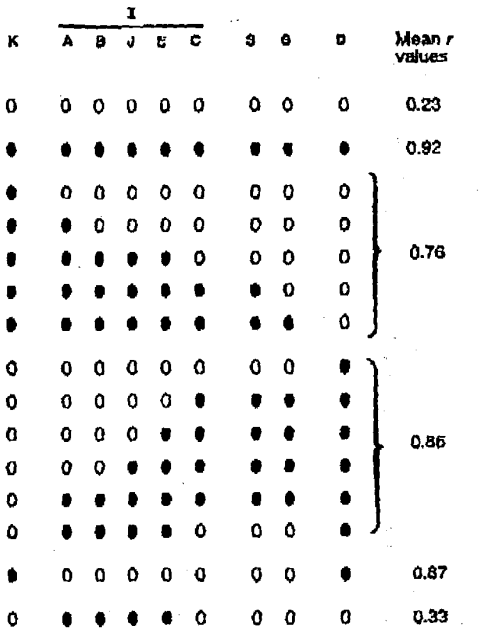

FIG. 2. Homing in lymph nodes according to identities (●) or differences (○). Labelled lymphocytes were injected intravenously into mice under different genetic conditions: allogenic (first line), syngenic (second line), congenic where the difference involves only one or several genes of the H-2 complex (all other lines). The average value of *r* (percentage of homing from which the control value has been deducted) is high wherever there is identity (●) with H-2D or H-2K; H-2I identity has no influence [66].

of one should correspond to the mutation and selection of the other. This is unlikely. Here again, however, one might envisage, according to Jerne's theory, that each individual has all possible receptors, the appropriate receptor being selected in early life, perhaps in the thymus. This is probably what occurs, for example, in the growth of allophenic mice in which cells carrying different H-2 antigens coexist.

Whatever the mechanism, the fact remains that self-recognition is a general and active phenomenon of any cell that is, at least partially, linked to the MHC. We suggest that class I products are responsible for individuality, for integrity, and perhaps for the general cohesion of the being and that class II products are an example of cellular cooperation, thanks to self-recognition at the level of the differentiated cells of the immune system, allowing the immune system to function harmoniously.

Future prospects

Thus the increasingly deep understanding of the MHC in man opens up exhilarating prospects both in public health and in basic science.

With regard to organ transplantation, we do not feel that the choice of the most compatible donor will be the last word. On the contrary, our aim must be to provoke in the recipient a specific tolerance to incompatible donor antigens without at the same time diminishing his or her immunological defences. It seems that with pre-operative transfusions the way has been opened to this type of preparation. We must now attempt to unravel its detailed mechanism so that the method can be used more generally. This will be the objective of the years to come, and we have no doubt that it will be achieved.

Although organ and bone marrow transplantations mark a milestone and have already brought help to numerous patients, they should not be considered an end in themselves. Etiological treatment should progressively replace them.

The discovery of more than 50 diseases associated with or linked to HLA is perhaps still more promising, and although the diagnostic or prognostic benefits to practising physicians are still limited, physicians recognize the validity of this approach. They know that correction of the abnormality which provokes a disease is close at hand when the gene responsible has been located and its function defined. Thanks to the astounding possibilities offered by genetic engineering it will henceforth be possible to know the exact DNA sequence in the vicinity of the HLA genes. The latter will serve as markers and will make it possible to discern anomalies of susceptibility genes. We must emphasize the possibility that in some cases no anomaly will be found because a gene (or combination of genes) may be perfectly active in the defence against certain antigens but totally inactive in the defence against others. Thus an inventory of the immunological capacities of each individual will need to be drawn up. This inventory will show the weaknesses (susceptibility), the excesses (autoimmunization), and the good capacities (protection) afforded by each type of gene combination. In this way, preventive medicine of high precision will be possible; a personalized medicine that will be more efficient and less burdensome for the community than the present mass system.

At the same time, researchers now have the means with which to approach the crucial problem represented by the subtle organization of man's immune system. The cascade of interrelationships, and the language used, between different immunocompetent cells will be clarified; the place of the 'specific' and the 'non-specific' will be recognized; the role of HLA products in messages between well-defined cells will be determined. This deeper understanding of man's immune response will quickly have major repercussions in pathology. It will perhaps provide the key to the irritating problem of the treatment of cancer, and may also provide a simple means of inducing graft tolerance at will. It will also perhaps lead to an immunological treatment of the major parasitic diseases that still afflict such a large part of mankind.

Finally, the discovery of the primary function of the molecules of the MHC found at the surface of all, or almost all, cells of the organism will be a decisive step in our understanding of the differentiation and social organization of cells.

The way already trod is but a simple introduction. There are still many marvellous pages to be written . . .

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Biography*

Jean Dausset's mother originated from Lorraine, and his father from the Pyrénées, two French provinces very distant from one another and with vast cultural differences. His parents met in Paris. During the First World War, his father, a doctor and captain in the army, sent Jean Dausset's mother and the first three children to Toulouse. It was there that Jean Dausset was born, on 19 October 1916, and this region has held a strong attraction for him ever since.

After the war, his father worked as a physiotherapist and radiologist, dividing his time between Paris and the spa towns. Jean Dausset spent his early childhood in Biarritz, until the age of secondary school. Then, when he was 11 years old, his family went to settle permanently in Paris. He pursued his secondary studies at the Lycée Michelet and obtained his baccalaureate in mathematics.

His choice of career was almost dictated by that of his father, Henri Dausset, who pioneered Rheumatology in France. His medical studies progressed without incident until the advent of the Second World War, when they were interrupted. He was mobilized in 1939 and returned from the French Campaign in 1940 to a Paris occupied by the German army. He began to devote his time ardently to the preparation of a competitive examination for the title of Intern of the Paris Hospitals. Upon receiving this title, he immediately left to join the fighting forces in North Africa. During the Tunisian Campaign, he performed blood transfusions in the army. This was his first introduction to immunohaematology.

While training in Algiers, he performed his first laboratory experiments and carried out his first scientific study on blood platelets.

On his return in 1944 to a liberated Paris, he was given the responsibility for collection of blood samples in the Paris area, working from the Regional Blood Transfusion Centre at Hôpital Saint-Antoine.

As soon as the war was over, he undertook his first real research study, in collaboration with Professor Marcel Bessis. Professor Bessis had just developed exchange-transfusion in new-born babies and adults. It is impossible to say how much time he spent treating, with this method, women who had become anuric following abortion manoeuvres resulting in septicaemia due to *Clostridium perfringens*—this was his first contact with kidney failure!

His clinical years were oriented towards haematology and paediatrics, with a constant attraction to the laboratory. In 1948, he was sent, as a French trainee, to the Children's Hospital in Boston (Professors L. K. Diamond and Sydney Farber) where he worked in one of the Harvard Medical School laboratories.

On his return to France, he took up work again at the Regional Blood Transfusion Centre, where he immediately became interested in the new immunohaematology techniques for red blood cells. He decided to transpose these techniques to white blood cells and platelets.

The principal observation of leuco-agglutination and thrombo-agglutination was made in 1952. Since that time, he has retained a constant interest in the immunogenetics of blood cells.

In 1958, while Head of the Immunohaematology Laboratory at the National Blood Transfusion Centre, he described the first leucocyte antigen, Mac, which later became known as HLA-A2.

Preoccupied with the state of medical research in France, he undertook, with Professor Robert Debré, to institute radical reforms in the hospital and university structures. This work as advisor to the cabinet of the National Ministry of Education spanned three consecutive years and culminated in the introduction of a law which established full-time employment in French hospitals, introducing to the hospitals Professors of Basic Sciences, who were given hospital responsibilities. This reform permitted a soar in French biology and brought a new lease of life to French medical research.

Despite the administrative struggles which ensued during this period, he never abandoned his laboratory work. In 1958, he was named Assistant Professor of Haematology at the Faculty of Medicine in Paris, then Professor of Haematology in 1963 and was appointed Head of the Immunology Department at Hôpital Saint-Louis. Again, he devoted his time entirely to research and, in 1965, described the first tissue group system (Hu-1, later named HLA).

Thanks to the admirable volunteer blood donors, skin donors and skin recipients, grafted under the care of Professor F. T. Rapaport, correlations were established between graft survival and tissue incompatibility.

He participated in the creation of the Research Institute on Blood Diseases, directed by Professor Jean Bernard, and was Assistant Director there until 1968. One of the departments under his direction was the Research Unit on Immunogenetics of Human Transplantation, an INSERM (National Institute of Health and Medical Research) unit of which he has been director since 1968.

In 1977, the Collège de France called him to the Chair of Experimental Medicine, a position held by Claude Bernard from 1958 to 1978, but his research laboratory remained at Hôpital Saint-Louis.

In 1963, he married Rose Mayoral from Madrid who gave him two children, Henri and Irène.

In addition to his scientific interests, he has only two passions in life: his family and modern plastic art.

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* This biography was written in 1980 when Jean Dausset received the Nobel Prize. Since that time, he has created, in Paris, the Human Polymorphism Study Center (Centre d'Etude du Polymorphisme Humain, CEPH) and set up an intensive international collaboration to establish a genetic map of the human genome.

Honours and prizes awarded

Professor Honoris Causa

University of Brussels	1977
University of Geneva	1977
University of Liège	1980

Member of Academies

Honorary foreign member of the Belgian Royal Academy of Medicine	1969
Académie des Sciences de l'Institut de France	1977
Académie de Médicine (Paris)	1977
Hon. Member, American Academy of Arts and Sciences (Boston)	1979
Hon. Member, Yugoslavian Academy of Arts and Sciences (Zagreb)	1979

Prizes

Grand Prix des Sciences Chimiques et Naturelles (Académie des Sciences)	1967
Médaille d'Argent du Centre National de la Recherche Scientifique	1967
Grand Prix Scientifique de la Ville de Paris	1968
Prix Cognac-Jay (Académie des Sciences de l'Institut de France)	1969
Stratton Lecture Award (USA)	1970
Landsteiner Award AABB, San Francisco (USA)	1970
Gairdner Foundation Prize (Canada)	1977
Koch Foundation Prize (Germany)	1978
Wolf Foundation Prize (Israel)	1978